

Terpinolene
[CASRN 586-62-9]

Review of Toxicological Literature

Prepared for

Scott Masten, Ph.D.
National Institute of Environmental Health Sciences
P.O. Box 12233
Research Triangle Park, North Carolina 27709
Contract No. N01-ES-65402

Submitted by

Raymond Tice, Ph.D.
Integrated Laboratory Systems
P.O. Box 13501
Research Triangle Park, North Carolina 27709

October 1999

EXECUTIVE SUMMARY

Terpinolene was nominated by NIEHS due to its high potential for human exposure.

Terpinolene is mainly used as a synthetic food flavoring additive or fragrance enhancer.

It is produced by the alcoholic sulfuric acid treatment of pinene or by fractionation of wood turpentine. The EPA OPPT High Production Volume Chemicals List records production of terpinolene to be between 3.4 and 4.5 million pounds in 1990 (approximately 1500 to 2000 metric tons).

There is a large body of information on the occurrence and persistence of terpinolene in the environment since it occurs naturally in many plant species and may be released by their decomposition or release of volatile oils into the atmosphere. Terpinolene has also been detected in emissions from gas- and steam-heated plywood veneer dryers. Terpinolene reacts readily with atmospheric oxidizing radicals and would not persist very long. If released into the soil, terpinolene would be expected to be strongly adsorbed and leaching through to the groundwater or volatilization would be unlikely. Studies have shown that biodegradation of terpinolene may occur in soil as well as in water. Its persistence in water is reduced by its volatilization, but its adsorption to sediment and suspended particulate matter may attenuate its volatilization from water.

Significant dietary exposure to terpinolene occurs through ingestion of such foods as ice cream and ices (64 ppm), candies (0.12 - 48 ppm), non-alcoholic beverages (16 ppm), and baked goods (49 ppm). It is also found as 9% of the distilled oil in commercial lime oils, which may account for some of the terpinolene in baked goods and other desserts. NIOSH estimated that nearly 50,000 workers were occupationally exposed to terpinolene in the 1970s and early 1980s. Inhalation of volatilized terpinolene can occur from some air fresheners. Dermal exposure can occur from such products as soaps (200 – 4000 ppm), lotions (100 – 1000 ppm), perfumes (1200 – 5000 ppm), and detergents (20 – 400 ppm).

Terpinolene is regulated by the Food and Drug Administration (FDA) as a synthetic food additive.

Terpinolene has low acute toxicity. Oral and dermal LD₅₀s are 3800 mg/kg (27.9 mmol/kg) in rats and mice and >5000 mg/kg (> 36 mmol/kg) in rabbits, respectively. Terpinolene was not irritating to the skin of 24 human volunteers when applied at a concentration of 20% in petrolatum for 48 hours under a closed patch. It is not a sensitizer in the maximization test. Eczematous lesions of the hands and forearms were reported by a woman using a machine cleaner containing terpinolene. Patch testing gave a positive reaction.

Terpinolene did not promote liver regeneration in partially hepatectomized rats.

Terpinolene also possesses fungicidal, insecticidal, and pheromone-like properties.

No information was found on metabolism, pharmacokinetics, acute and subchronic toxicity, chronic toxicity, synergistic or antagonistic activities, reproductive and developmental toxicity, carcinogenicity, genotoxicity, immunotoxicity or structure-activity relationships of terpinolene.

TABLE OF CONTENTS

EXECUTIVE SUMMARY.....	i
1.0 BASIS FOR NOMINATION.....	1
2.0 INTRODUCTION.....	1
2.1 Chemical Identification and Analytical Methods.....	1
2.2 Physical-Chemical Properties	1
2.3 Commercial Availability	2
3.0 PRODUCTION PROCESSES	2
4.0 PRODUCTION AND IMPORT VOLUMES	2
5.0 USES	2
6.0 ENVIRONMENTAL OCCURRENCE AND PERSISTENCE	3
7.0 HUMAN EXPOSURE.....	4
8.0 REGULATORY STATUS.....	6
9.0 TOXICOLOGICAL DATA.....	6
9.1 General Toxicology.....	6
9.1.1 Human Data.....	6
9.1.2 Chemical Disposition, Metabolism, and Toxicokinetics	6
9.1.3 Acute Exposure.....	7
9.1.4 Short-Term and Subchronic Exposure	7
9.1.5 Chronic Exposure.....	7
9.1.6 Synergistic and Antagonistic Activities	7
9.2 Reproductive and Teratological Effects	7
9.3 Carcinogenicity	7
9.4 Initiation/Promotion Carcinogenicity Studies	8
9.5 Anticarcinogenicity	8
9.6 Genotoxicity	8
9.7 Cogenotoxicity	8
9.8 Antigenotoxicity.....	8
9.9 Immunotoxicity.....	8
9.10 Other Data.....	8
10.0 STRUCTURE-ACTIVITY RELATIONSHIPS.....	9

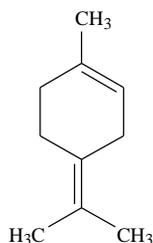
11.0	ONLINE DATABASES AND SECONDARY REFERENCES	10
11.1	Online Databases	10
11.2	Secondary References	11
12.0	REFERENCES	11
13.0	REFERENCES CONSIDERED BUT NOT CITED	13
	ACKNOWLEDGEMENTS.....	14
APPENDIX A	UNITS AND ABBREVIATIONS	A-1
APPENDIX B	PHYTOCHEMICAL AND ETHNOBOTANICAL DATABASE RESULTS FOR TERPINOLENE.....	B-1
TABLES		
Table 1	Half-life of Terpinolene When Exposed to Various Atmospheric Radicals	4
Table 2	Regulations Relevant to Terpinolene	6
Table 3	Acute Toxicity Values for Terpinolene	7

1.0 BASIS FOR NOMINATION

Terpinolene was nominated by NIEHS due to its high potential for human exposure.

2.0 INTRODUCTION

Terpinolene
[CASRN 586-62-9]



2.1 Chemical Identification

The monoterpene terpinolene (C₁₀H₁₆; mol. wt. = 136.24) is also called:

Cyclohexene, 1-methyl-4-(1-methylethylidene)-
4-Isopropylidene-1-methylcyclohexene
p-Mentha-1,4(8)-diene
p-Mentha-2,4(8)-diene
1-Methyl-4-isopropylidene-1-cyclohexene
1,4(8)-Terpadiene
Terpinolen

Terpinolene can be determined by gas chromatography (RIFM no. 75-132) or by infrared spectroscopy (RIFM no. 75-132) (Opdyke, 1988). Terpinolene is a highly flammable compound and, in air, may form explosive mixtures (HSDB, 1998). Terpinolene is known to polymerize readily (Furia and Bellanca, 1971).

2.2 Physical-Chemical Properties

Property	Information	Reference
Physical State	Colorless to very pale, straw-yellow, oily liquid	Furia and Bellanca (1971)
Odor	Sweet, pine-like odor	Furia and Bellanca (1971)
Taste	Somewhat sweet, citrus flavor	Furia and Bellanca (1971)
Boiling Point (°C)	185 at 760 mm Hg	Weast and Astle (1980)
Density (20 °C/4 °C)	0.8623	Weast and Astle (1980)
Soluble in	ethanol, alcohol, and benzene	Weast and Astle (1980)
Water Solubility	2 mg/L (estimated)	Esposito (1999)
Vapor Pressure (mmHg at 25 °C)	0.595	HSDB (1998)
Flash Point (°C)	37.222	HSDB (1998)

2.3 Commercial Availability

Technical and perfume/fragrance grades of terpinolene are available from Glidco Inc. in tank car, tank truck, and 55-gallon drums (Chemyclopedia Online, 1999). All grades of terpinolene are available from Penta Manufacturing Co. (Fairfield, NJ) in 1- and 5-gallon pails.

Other terpinolene suppliers include:

Aldrich Chemical Company, Inc. *	Milwaukee, WI
Advanced Synthesis Technologies *	San Ysidro, CA
Berje Chemical Products, Inc.	Bloomfield, NJ
Bush Boake Allen, Inc. *	Montvale, NJ
Fluka Chemical Company Ltd.*	Oakville, Ontario
Indofine Chemical Company, Inc.	Belle Mead, NJ
Millennium Specialty Chemicals *	Jacksonville, FL
TCI America, Inc.	Portland, OR

*Bulk suppliers

Source: Chemical Sources International. *Chem. Sources-U.S.A.* (1999)

3.0 PRODUCTION PROCESSES AND ANALYSES

Terpinolene is produced by the alcoholic sulfuric acid treatment of pinene (Opdyke, 1988). It can also be isolated by fractionation of wood turpentine (Lewis, 1993).

4.0 PRODUCTION AND IMPORT VOLUME

Terpinolene is produced by Millennium Specialty Chemicals, Inc., located in Jacksonville, FL (SRI, 1998). U.S. production was probably greater than 2.27×10^6 grams (2.3 tons) in 1979 and 1981 (HSDB, 1998). The EPA OPPT High Production Volume Chemicals List records production of terpinolene to be between 3.0 and 4.0 million pounds (14,000 to 18,000 metric tons) per year (U.S. EPA, 1998).

5.0 USES

Terpinolene is mainly used as a synthetic food flavoring additive or fragrance enhancer. It is used as a flavor additive in artificial essential oils, fruits, citrus, ice cream, non-alcoholic beverages, candy, and baked goods (Furia, 1980; Furia and Bellanca, 1971). Its use in fragrances is reported to exceed 50,000 pounds per year (Opdyke, 1988).

Terpinolene is used in the emulsion polymerization of acrylonitrile-butadiene-styrene (ABS) plastics (Morneau et al., 1978), acting as a chain-transfer agent in the blend of high-butadiene-content ABS with styrene-acrylonitrile (SAN) copolymer.

Terpinolene has been tested as a possible agent for the enhancement of transdermal drug delivery (Kitahara et al., 1993; Monti et al., 1995). Terpinolene, in mixtures with other terpenes, has been patented as gall stone solvents (Opdyke, 1988).

6.0 ENVIRONMENTAL OCCURRENCE AND PERSISTENCE

Terpinolene is reported to be a minor constituent of a few essential oils. It is present in the oil of nutmeg and mace, both of which are derived from *Myristica fragrans* (Forest and Heacock, 1987). It is a minor constituent of *Manilla elemi*, several commercially important tree species, *Nectandra elaiophora*, and *Dacrydium colensoi* (Furia and Bellanca, 1971). A list of plant species containing terpinolene, the parts of the plants where it is primarily found, and the relative amounts are provided in **Appendix B**.

Analysis of emissions from several gas- and steam-heated plywood veneer dryers in the U.S. revealed that 96-97% of the gaseous emissions from the dryer stacks that processed veneer from larch, white fir, red fir, and loblolly pine consisted of terpenes, with 0.3 to 1.9% of the detected terpenes consisting of terpinolene (Cronn et al., 1983). Other Swedish studies also detected elevated levels of terpinolene in the vicinity of forestry operations (Strömvall, 1992; Strömvall and Petersson, 1991; and Strömvall and Petersson, 1993).

Terpinolene would exist almost entirely as a vapor in the atmosphere considering its vapor pressure of 0.595 mmHg at 25 °C (HSDB, 1998). It is not expected to degrade by photolysis in the atmosphere since terpinolene does not absorb sunlight (HSDB, 1998). Terpinolene is highly reactive in a number of photooxidation reactions that occur in the atmosphere so it is not expected to persist very long (HSDB, 1998). The half-life estimates of the reaction of terpinolene in the atmosphere with three photooxidants are given in the following table.

If released to the soil, terpinolene is expected to be strongly adsorbed due to its estimated K_{oc} of 4766 (HSDB, 1998). Since it would remain relatively immobile in the soil, it would not be expected to leach through the soil and into the groundwater. Terpinolene's strong adsorption to soil would limit its volatilization there, even though its estimated Henry's Law Constant of

0.0614 atm-cu m/mole suggests that it may volatilize readily from moist near surface soils (HSDB, 1998).

Terpinolene would be expected to biodegrade in soil, with the process being accelerated in acclimated soils (Misra et al., 1996). Biodegradability in wastewater was variable (Wilson and Hrutfiord, 1975, cited by HSDB, 1998).

Terpinolene would be expected to rapidly volatilize in water based on an estimated half-life of 3.4 hours for volatilization from a model river (HSDB, 1998). Adsorption to sediment and suspended particulate matter may attenuate the volatilization of terpinolene from water based on the estimated half-life of 41 days in an average pond (HSDB, 1998). Photolysis is not a means of degradation in water since molecules similar to terpinolene which possess isolated double bonds do not absorb light at wavelengths above 290 nm. There are no studies that would determine the rate of biodegradation in water, if any, that would exist under controlled or laboratory conditions; however, the earlier mentioned study of treated wastewater from kraft paper mills would suggest that biodegradation might occur in water.

Table 1. Half-life of Terpinolene When Exposed to Various Atmospheric Radicals

Radicals	Atmospheric Concentration of the Radicals (per cm ³)	Half-life of Terpinolene (minutes)
Hydroxyl	5 x 10 ⁵	84.0
Ozone	7 x 10 ¹¹	1.7 – 23.0
Nitrate	2.4 x 10 ⁸	1.0

Taken from HSDB (1998)

7.0 HUMAN EXPOSURE

Human exposure is usually by ingestion of foods containing terpinolene as a flavor enhancer or by dermal contact with or inhalation of terpinolene used as a fragrance additive. Exposure to terpinolene is likely to occur as a result of incidental exposure from use (solvents, flavorings, manufacture of synthetic resins) or disposal, natural plant emission from degradation and respiration, and natural forest products industry atmospheric emissions. Exposure may occur from its presence in soil, water, and air.

The usual concentrations of terpinolene as a fragrance additive are the following: 200 ppm in soaps, 20 ppm in detergents, 100 ppm in creams and lotions, and 1200 ppm in perfumes (Opdyke, 1988). However, the concentration in these products could reach a maximum of 4000 ppm in soaps, 400 ppm in detergents, 1000 ppm in creams and lotions, and 5000 ppm in perfumes.

As a flavor additive, terpinolene may be found in non-alcoholic beverages (16 ppm), ice cream and ices (64 ppm), candy (0.12 – 48 ppm), and baked goods (49 ppm) (Furia and Bellanca, 1971). Terpinolene is a 9% constituent of commercial distilled lime oils, which may account for its presence in baked goods and other desserts (Mookherjee and Wilson, 1996).

Many foods have naturally occurring levels of terpinolene. Terpinolene has been detected in the mixture of volatile constituents of mangoes (2.0 µg/g) grown in Florida and stored in a deep freezer (-15 °C) for 14 months (MacLeod and Snyder, 1988; cited by HSDB, 1998). The terpinolene concentration in fresh mango fruit was found to be 1.1 µg/g. Terpinolene has also been detected in a variety of nectarines; Sunfire nectarines were found to have a concentration of 10 ppb (Engel et al., 1988; Takeoka et al., 1988; both cited by HSDB, 1998). For more information about the plants and fruit that contain terpinolene see **Appendix B**.

Terpinolene was also found in 12 of 22 samples of commercial gins (Villalon-Mir et al., 1985).

NIOSH estimated that, between 1972 and 1974, 49,927 workers were potentially exposed to terpinolene in the United States (NIOSH, 1974; Cited by HSDB, 1999). NIOSH has estimated that, between 1981 and 1983, 47,312 workers were potentially exposed to terpinolene in the United States (NIOSH, 1983; cited by HSDB, 1998).

Natural release of terpinolene from U.S. woodlands also may contribute to human exposure. Terpinolene is frequently emitted from some trees into the environment (Zimmerman, 1979; cited by Guenther et al., 1994). Monoterpene release is highest in U.S. forests located in the Southeast and Northwest (Guenther et al., 1994). High monoterpene emissions have been measured in forests containing Northwest conifers, Western pines, Douglas firs, and Southern pines. For a list of plant species and their relative terpinolene content, see **Appendix B**.

8.0 REGULATORY STATUS

Terpinolene was given the status of a “generally regarded as safe” (GRAS) direct food additive by the Flavor Extract Manufacturers Association (FEMA No. 3046) in 1965 and is approved by the FDA for use in foods (Opdyke, 1988). It may be used alone or in combination with flavoring substances or adjuvants generally recognized as safe in food, prior sanctioned for such use, or designated by an appropriate section in Part 172.

The Council of Europe included terpinolene in the list of artificial food flavoring substances that may be added to food without risk to human health in 1974 (Opdyke, 1988).

U. S. government regulations pertaining to terpinolene are summarized below.

Table 2. Regulations Relevant to Terpinolene

	Regulation	Summary of Regulation
F D A	21 CFR 172.515	<p>Terpinolene is regulated by the FDA as a synthetic flavoring substance and adjuvant. Synthetic flavoring substances may be safely used in foods in accordance with the following conditions:</p> <p>a) They are used in the minimum quantity required to produce their intended effect and otherwise in accordance with all the principles of good manufacturing practice.</p> <p>b) They may be used alone or in combination with flavoring substances or adjuvants generally recognized as safe in food, prior sanctioned for such use, or designated by an appropriate section in Part 172.</p>

9.0 TOXICOLOGICAL DATA

9.1 General Toxicology

9.1.1 Human Data

Terpinolene was not irritating to human skin when applied at a concentration of 20% in petrolatum for 48 hours under a closed patch in 24 volunteers, and it was not a sensitizer in the maximization test (Opdyke, 1988). However, in a case report and was reported that a 49-year-old woman developed eczematous lesions of the hands and forearms using a machine cleaner containing terpinolene (Castelain et al., 1980). Upon patch testing, terpinolene gave a positive reaction.

9.1.2 Chemical Disposition, Metabolism, and Toxicokinetics

No metabolic or toxicokinetic studies were identified for terpinolene.

9.1.3 Acute Exposure

Acute toxicity values for terpinolene are presented in **Table 3**.

Terpinolene was not irritating in rabbits when applied to intact or abraded skin with an occluded patch for 24 hours (Opdyke, 1988). Using a commercial air freshener containing at least 14 ingredients, one of which was terpinolene, Anderson and Anderson (1997) found the LD₅₀ in male Swiss-Webster mice for the product to be approximately 640 ppm. This is based on the total volatile organic chemicals in the exposure chamber during a series of exposure concentrations.

Table 3. Acute Toxicity Values for Terpinolene

Route	Species (sex and strain n.p.)	LD ₅₀	Reference
Oral	Rat	4.39 mL/kg (3790 mg/kg)	Opdyke (1988)
	Mouse	4.40 mL/kg (3800 mg/kg)	Opdyke (1988)
Dermal	Rabbit	>5.79 mL/kg (>5000 mg/kg)	Opdyke (1988)

Abbreviations: n.p. = not provided; LD₅₀ = dose lethal to 50% of the test animals

9.1.4 Short-Term and Subchronic Exposure

No short-term or subchronic toxicity studies were identified for terpinolene.

9.1.5 Chronic Exposure

No chronic toxicity studies were identified for terpinolene

9.1.6 Synergistic and Antagonistic Activities

No synergistic or antagonistic activity studies were identified for terpinolene

9.2 Reproductive and Teratological Effects

No reproductive or teratological studies were identified for terpinolene.

9.3 Carcinogenicity

No carcinogenicity studies were identified for terpinolene

9.4 Initiation/Promotion Studies

No initiation or promotion studies were identified for terpinolene

9.5 Anticarcinogenicity

No anticarcinogenicity studies were identified for terpinolene

9.6 Genotoxicity

No genotoxicity studies were identified for terpinolene

9.7 Cogenotoxicity

No cogenotoxicity studies were identified for terpinolene

9.8 Antigenotoxicity

No antigenotoxicity studies were identified for terpinolene.

9.9 Immunotoxicity

No immunotoxicity studies were identified for terpinolene other than the human dermal sensitization studies mentioned in **Section 9.1.1**.

9.10 Other Data

Many monoterpenes are now being studied for their fungicidal and insectidal properties. Terpinolene has been shown to be effective against budworm larval growth (Zou and Cates, 1997). It has also been shown effective against fungal spores of *Diplodia pinea* (Chou and Zabkiewicz, 1976).

Terpinolene has also been observed to possess pheromone-like properties in some insects. It is an alarm pheromone found in the cephalic secretions of the Australian termite (Buckingham, 1994; Castelain et al., 1980). Terpinolene, when evaluated in a bioassay as a bait for beetle traps, was found to attract both sexes of the western balsam bark beetle at a dose of 1 mg (0.0073 mmoles).

Terpinolene also exhibits antibacterial properties. It was shown to be effective against one of the bacteria that cause acne, *Propionibacterium acnes*, at a concentration of 50 µg/mL (Kubo et al., 1994).

Terpinolene was tested for its effect on promoting liver regeneration in partially hepatectomized rats (Gershbein, 1977). Little difference was seen in liver regeneration between the treated group, given 2450-2950 mg/kg (17.98 – 21.65 mmol/kg) by subcutaneous injection, and the control groups.

10.0 STRUCTURE-ACTIVITY RELATIONSHIPS

No structure-activity relationship information was identified for terpinolene.

11.0 ONLINE DATABASES AND SECONDARY REFERENCES**11.1 Online Databases**Chemical Information System Files

SANSS (Structure and Nomenclature Search System)

TSCATS (Toxic Substances Control Act Test Submissions)

National Library of Medicine Databases

EMIC and EMICBACK (Environmental Mutagen Information Center)

STN International Files

BIOSIS

CANCERLIT

CAPLUS

EMBASE

HSDB

MEDLINE

Registry

RTECS

TOXLINE

TOXLINE includes the following subfiles:

Toxicity Bibliography	TOXBIB
International Labor Office	CIS
Hazardous Materials Technical Center	HMTC
Environmental Mutagen Information Center File	EMIC
Environmental Teratology Information Center File (continued after 1989 by DART)	ETIC
Toxicology Document and Data Depository	NTIS
Toxicological Research Projects	CRISP
NIOSHTIC [®]	NIOSH
Pesticides Abstracts	PESTAB
Poisonous Plants Bibliography	PPBIB
Aneuploidy	ANEUPL
Epidemiology Information System	EPIDEM
Toxic Substances Control Act Test Submissions	TSCATS
Toxicological Aspects of Environmental Health	BIOSIS
International Pharmaceutical Abstracts	IPA
Federal Research in Progress	FEDRIP
Developmental and Reproductive Toxicology	DART

In-House Databases

CPI Electronic Publishing Federal Databases on CD
Current Contents on Diskette®
The Merck Index, 1996, on CD-ROM

11.2 Secondary References

Weast, R.C., and M.J. Astle. 1980. CRC Handbook of Chemistry and Physics: A Ready-Reference Book of Chemical and Physical Data. 61st ed. Chemical Rubber Company (CRC) Press:Boca Raton, FL. p. C-583.

12.0 REFERENCES

American Chemical Society. 1999. Chemyclopedia Online.
<http://pubs3.acs.org:8899/chemcy/>. Last accessed May 4, 1999.

Anderson, A.C., and J.H. Anderson. 1997. Toxic effects of air freshener emissions. Arch. Environ. Health 52:433-441.

Buckingham, J. 1994. Dictionary of Natural Products. Chapman & Hall, New York, NY. p. 3819.

Castelain, P.-Y., J.P. Camoin, and J. Jouglard. 1980. Contact dermatitis to terpene derivatives in a machine cleaner. Contact Dermatitis 6:358-360.

Chemical Sources International. 1999. Chem Sources, U.S.A. Edition. Chemical Sources International, Clemson, SC. p. 915.

Chou, C.K.S., and J.A. Zabkiewicz. 1976. Toxicity of monoterpenes from *Pinus radiata* cortical oleo resin to *Diplodia pinea* spores. Eur. J. For. Pathol. 6:354-359. Abstract.

Cronn, D.R., S.G. Truitt, and M.J. Campbell. 1983. Chemical characterization of plywood veneer dryer emissions. Atmos. Environ. 17:201-212.

Duke, J.A. Dr. Duke's Phytochemical and Ethnobotanical Databases. <http://www.ars-grin.gov/cgi-bin/duke/>. Last accessed May 4, 1999.

Esposito, R. 1999. Genium's Handbook of Safety, Health, and Environmental Data for Common Hazardous Substances. Genium Publishing, Schenectady, NY. p. 3281-3282.

Forrest, J.E., and R.A. Heacock. 1972. Nutmeg and mace, the psychotropic spices from *Myristica fragrans*. Lloydia 35:440-449.

Furia, T.E. 1980. CRC Handbook of Food Additives. Vol. 2. CRC Press:Boca Raton, FL. pg. 302.

Furia, T.E., and N. Bellanca. 1971. Fenaroli's Handbook of Flavor Ingredients. CRC Press, Boca Raton, FL. pg. 617.

Gershbein, L.L. 1977. Regeneration of rat liver in the presence of essential oils and their components. *Food Cosmet. Toxicol.* 15:173-181.

Guenther, A., P. Zimmerman, and M. Wildermuth. 1994. Natural volatile organic compound emission rate estimates for U.S. woodland landscapes. *Atmos. Environ.* 28:1197-1210.

Kitahara, M., F. Ishiguro, K. Takayama, K. Isowa, and T. Nagai. 1993. Evaluation of skin damage of monoterpenes, percutaneous absorption enhancers, by using cultured human skin cells. *Biol. Pharm. Bull.* 16:912-916.

Kubo, I., H. Muroi, and A. Kubo. 1994. Naturally occurring antiacne agents. *J. Natur. Prod.* 57:9-17.

Misra, G., and S.G. Pavlostathis. 1997. Biodegradation kinetics of monoterpenes in liquid and soil-slurry systems. *Appl. Microbiol. Biotechnol.* 47:572-577.

Misra, G., S.G. Pavlostathis, E.M. Perdue, and R. Aruajo. 1996. Aerobic biodegradation of selected monoterpenes. *Appl. Microbiol. Biotechnol.* 45:831-838.

Monti, D., M.F. Saettone, B. Giannaccini, and D. Galli-Angeli. 1995. Enhancement of transdermal penetration of dapiprazole through hairless mouse skin. *J. Controlled Release* 33:71-77.

Mookherjee, B.D., and R.A. Wilson. 1993. Oils, Essential. In: *Kirk-Othmer Encyclopedia of Chemical Technology*. 4th Edition. Kroschwitz, J.I., and M. Howe-Grant (Eds). John Wiley & Sons, New York, NY. pp. 603-674.

Morneau, G.A., W.A. Pavelich, and L.G. Roettger. 1981. ABS Resins. In: *Kirk-Othmer Encyclopedia of Chemical Technology*. Third Edition. Gryson, M., and D. Eckroth. (eds.). John Wiley & Sons, New York, NY. ps. 442-456.

Opdyke, D.L.J. 1988. Fragrance raw materials monographs: Terpinolene. *Food Cosmet. Toxicol.* 14(Suppl.):877-878.

SRI International. 1998. Directory of Chemical Producers. United States of America. Stanford Research Institute International, Menlo Park, CA. p. 644.

Stromvall, A.-M. 1992. Terpenes emitted to air from forestry and the forest industry. *Govt. Report Announcements & Index (GR&I)*. No12, NTIS/DE4730409. 25 pp.

Stromvall, A.-M., and G. Petersson. 1991. Conifer Monoterpenes emitted to the air by logging operations. *Scand. J. For. Res.* 6:253-258.

Stromvall, A.-M., and G. Petersson. 1993. Photooxidant-forming monoterpenes in air plumes from kraft pulp industries. *Environ. Pollut.* 79:219-223.

U.S. Environmental Protection Agency (EPA). 1998. OPPT High Production Volume Chemicals Database. <http://www.epa.gov/oppintr/chemtest/hpv.htm>. Last accessed June 30, 1998.

Villalon-Mir, M., G. Lopez, H.L. De La Serrana, M.D.C. Lopez-Martinez, and R. Garcia-Villanova. 1985. A comparative study of gas chromatography of alcohols, aldehydes, esters, and essential components which make up a standard gin and those from other commercial gins. *An. Bromatol.* 36:61-69. Abstract.

Zou, J., and R.G. Cates. 1997. Effects of terpenes and phenolic and flavonoid glycosides from Douglas fir on western spruce budworm larval growth, pupal weight, and adult weight. *J. Chem. Ecol.* 23:2313-2326. Abstract.

13.0 REFERENCES CONSIDERED BUT NOT CITED

Atkinson, R., D. Hasegawa, and S.M. Aschmann. 1990. Rate constants for the gas phase reactions of ozone with a series of monoterpenes and related compounds at 296 plus or minus 2K. *Int. J. Chem. Kinet.* 22:871-887. Abstract.

Japar, S.M., C.H. Wu, and H. Niki. 1974. Rate constants for the gas phase reaction of ozone with alpha-pinene and terpinolene. *Environ. Lett.* 7:245-249.

Larsen, B.R., M. Lahaniati, A. Calogirou, and D. Kotzias. 1998. Atmospheric oxidation products of terpenes: a new nomenclature. *Chemosphere* 37:1207-1220.

Lewis, R.J. 1992. *Sax's Dangerous Properties of Industrial Materials*. Eighth Edition. Van Nostrand Reinhold, New York, NY. p.3196.

Li, J., and E.M. Perdue. 1995. Physiochemical properties of selected monoterpenes. *Abstr. Pap. Am. Chem. Soc.* 209(1-2):ENVR 183.

Platt, A.E., and T.C. Wallace. 1981. Styrene Plastics. In: *Kirk-Othmer Encyclopedia of Chemical Technology*. Third Edition. Gryson, M., and D. Eckroth. (eds.). John Wiley & Sons, New York, NY. ps.801-847.

Ragab, M., and S.E. El-Nemr. 1990. Chemical composition and volatile constituents of canned mango juice. *Nahrung* 34:591-599. Abstract.

Rogers, J.A., Jr. 1981. Oils Essential. In: *Kirk-Othmer Encyclopedia of Chemical Technology*. Third Edition. Gryson, M., and D. Eckroth. (eds.). John Wiley & Sons, New York, NY. ps.307-332.

Schuetzle, D., and R.A. Rasmussen. 1978. The molecular mechanism of secondary aerosol particles formed from terpenes. *J. Air Pollut. Contr. Assoc.* March 1978:236-240.

Wilkins, K. 1994. Volatile organic compounds from household waste. *Chemosphere* 29:47-53.

ACKNOWLEDGEMENTS

Support to the National Toxicology Program for the preparation of Terpinolene — Draft Review of Toxicological Literature was provided by Integrated Laboratory Systems, Inc., through NIEHS Contract Number N01-ES-65402. Contributors included: Raymond R. Tice, Ph.D. (Principal Investigator); Bonnie L. Carson, M.S. (Co-Principal Investigator); John W. Winters, B.S.; and Claudine A. Gregorio, M.A..

APPENDIX A

UNITS AND ABBREVIATIONS

APPENDIX A UNITS AND ABBREVIATIONS

°C = degrees Celsius

mg/kg = milligram(s) per kilogram

mg/L = milligram(s) per liter

ml/kg = milliliter(s) per kilogram

mm Hg = millimeter(s) of mercury

mol. wt. = molecular weight

n.p. = not provided

ppm = parts per million

Appendix B

Phytochemical and Ethnobotanical Database Results for Terpinolene

Phytochemical and Ethnobotanical Database

Plants Containing Terpinolene

Ordered by quantity

Species	Part	Quantity (ppm)
<i>Pastinaca sativa</i> L. -- Parsnip	Root Essent. Oil	666,000
<i>Melaleuca alternifolia</i> CHEEL -- Tea-Tree	Leaf	236-6,125
<i>Myristica fragrans</i> HOUTT. -- Mace, Nutmeg	Seed	2,720
<i>Apium graveolens</i> L. -- Celery	Fruit Essent. Oil	2,000
	Leaf Essent. Oil	2,000
<i>Daucus carota</i> L. -- Carrot	Root	1,520
<i>Canarium indicum</i> L. -- Java-Olive, Manila Elemi	Essential Oil	1,500
<i>Petroselinum crispum</i> (MILLER) NYMAN ex A. W. HILL -- Parsley	Seed	700
<i>Illicium verum</i> HOOK. f. -- Star-Anise	Fruit	435
<i>Origanum majorana</i> L. -- Marjoram	Plant	430
<i>Melaleuca linariifolia</i> SMITH -- Paperbark Tea tree	Leaf	600-750
<i>Rosmarinus officinalis</i> L. -- Rosemary	Plant	350
<i>Juniperus communis</i> L. -- Common Juniper, Juniper	Fruit	320
<i>Foeniculum vulgare</i> MILLER -- Fennel	Plant	230
<i>Hedeoma reverchonii</i> GRAY -- Reverchon's Pennyroyal	Plant	222
<i>Laurus nobilis</i> L. -- Bay	Leaf	200
<i>Eucalyptus citriodora</i> HOOK. -- Lemon Eucalyptus	Leaf	160
<i>Monarda didyma</i> L. -- Beebalm, Oswego Tea	Plant	160
<i>Umbellularia californica</i> (HOOK. & ARN.) NUTT. -- California Bay	Plant	160
<i>Citrus aurantiifolia</i> (CHRISTM.) SWINGLE -- Lime	Fruit	120
<i>Citrus limon</i> (L.) BURMAN f. -- Lemon	Essential Oil	120

Ethnobotanical and Phytochemical Database Results for Terpinolene (Continued)

Species	Part	Quantity (ppm)
<i>Salvia officinalis</i> L. -- Sage	<i>Plant</i>	112
<i>Satureja obovata</i> LAG. -- Iberian Savory, Savory	<i>Leaf</i>	0-215 0-190
<i>Mentha pulegium</i> L. -- European Pennyroyal	<i>Plant</i>	90
<i>Zingiber officinale</i> ROSCOE -- Ginger	<i>Rhizome</i>	90
<i>Origanum sipyleum</i> L. -- Bayircayi, Guveyoto	<i>Shoot</i>	0-170
<i>Satureja obovata</i> LAG. -- Iberian Savory, Savory	<i>Leaf</i>	0-170
<i>Cymbopogon nardus</i> (L.) RENDLE -- Ceylon Citronella, Citronella	<i>Plant</i>	84
<i>Pycnanthemum loomisii</i> NUTT. -- Loomis' Mountain Mint	<i>Shoot</i>	84
<i>Thymus saturejoides</i> -- Moroccan Savory Thyme	<i>Shoot</i>	0-150
<i>Foeniculum vulgare</i> MILLER -- Fennel	<i>Fruit</i>	60
<i>Thymus longicaulis</i> C. PRESL -- Kekik, Tas Kekik	<i>Shoot</i>	0-120
<i>Picea mariana</i> (MILLER) B.S.P. -- Black Spruce	<i>Twig</i>	46
<i>Lepechinia calycina</i> EPLING -- Epling's Lepechinia	<i>Plant</i>	45
<i>Sideritis mugronensis</i>	<i>Leaf</i>	5-90
<i>Cinnamomum verum</i> J. PRESL -- Cinnamon	<i>Bark</i>	44
<i>Micromeria teneriffae</i>	<i>Leaf</i>	0-80
<i>Rosmarinus x lavandulaceus</i> DE NOE -- Lavender Rosemary	<i>Shoot</i>	19-80
<i>Satureja douglasii</i> (BENTH.) BRIQ. -- Douglas' Savory	<i>Plant</i>	39
<i>Abies alba</i> MILLER -- Silver-Fir	<i>Leaf</i>	38
<i>Petroselinum crispum</i> (MILLER) NYMAN ex A. W. HILL -- Parsley	<i>Leaf</i>	33
<i>Origanum onites</i> L. -- Oregano, Pot Marjoram	<i>Shoot</i>	0-65
<i>Rosmarinus officinalis</i> L. -- Rosemary	<i>Shoot</i>	19-65 25-65
<i>Origanum onites</i> L. -- Oregano, Pot Marjoram	<i>Shoot</i>	0-60
<i>Thymus capitatus</i> (L.) HOFFM. -- 'Sicilian' Thyme, Spanish Origanum, Spanish Thyme	<i>Plant</i>	30

Ethnobotanical and Phytochemical Database Results for Terpinolene (Continued)

Species	Part	Quantity (ppm)
<i>Lavandula latifolia</i> MEDIK. -- Aspic, Broad-Leaved Lavender, Spike Lavender	<i>Plant</i>	28
<i>Ocimum tenuiflorum</i> L. -- Anise-Scented Basil	<i>Leaf</i>	0-55
<i>Pimenta dioica</i> (L.) MERR. -- Allspice	<i>Leaf</i>	27
<i>Coriandrum sativum</i> L. -- Coriander	<i>Fruit</i>	26
<i>Rosmarinus officinalis</i> L. -- Rosemary	<i>Shoot</i>	25-50
<i>Cinnamomum camphora</i> (L.) NEES & EBERM. -- Camphor, Ho Leaf	<i>Leaf</i>	24
<i>Hyssopus officinalis</i> subsp. <i>aristatus</i> (GODR.) BRIQ. -- Hyssop	<i>Shoot</i>	0-47.5
<i>Origanum syriacum</i> L. -- Za'Atar	<i>Shoot</i>	0-45
<i>Ocimum basilicum</i> L. -- Basil	<i>Plant</i>	22
<i>Hyssopus officinalis</i> L. -- Hyssop	<i>Leaf</i>	20
<i>Hyssopus officinalis</i> subsp. <i>aristatus</i> (GODR.) BRIQ. -- Hyssop	<i>Shoot</i>	0-40
<i>Mentha longifolia</i> (L.) HUDS. -- Biblical Mint	<i>Shoot</i>	20
<i>Pycnanthemum tenuifolium</i> SCHRAD. -- Slenderleaf Mountain Mint	<i>Shoot</i>	20
<i>Rosmarinus tomentosus</i> HUBER-MORATH & MAIRE -- Hairy Rosemary	<i>Shoot</i>	16-40
<i>Satureja thymbra</i> L. -- Goat Oregano	<i>Shoot</i>	0-37
<i>Litsea glaucescens</i> var. <i>glaucescens</i> -- Mexican bay	<i>Shoot</i>	30-35
<i>Origanum sipyleum</i> L. -- Bayircayi, Guveyoto	<i>Shoot</i>	0-35
<i>Rosmarinus eriocalyx</i> JORDAN & FOURR. -- Rosemary	<i>Shoot</i>	11-35
<i>Thymus riatarum</i> HUMBERT & MAIRE -- Moroccan' Thyme	<i>Shoot</i>	0-35
<i>Rosmarinus x mendizabalii</i> SAGREDO EX ROSUA -- Mendizabali's Rosemary	<i>Shoot</i>	16-33
<i>Angelica archangelica</i> L. -- Garden Angelica	<i>Root</i>	16
<i>Origanum vulgare</i> L. -- Common Turkish Oregano, Wild Oregano	<i>Plant</i>	16
<i>Monarda didyma</i> L. -- Beebalm, Oswego Tea	<i>Leaf</i>	15

Ethnobotanical and Phytochemical Database Results for Terpinolene (Continued)

Species	Part	Quantity (ppm)
<i>Thymus broussonettii</i> BOISS. -- Moroccan Thyme	<i>Shoot</i>	0-30
<i>Origanum minutiflorum</i> O. SCHWARZ & P.H. DAVIS -- Small-Flowered Oregano	<i>Shoot</i>	20-27
<i>Rosmarinus eriocalyx</i> JORDAN & FOURR. -- Rosemary	<i>Shoot</i>	5-26
<i>Thymus cilicicus</i> BOISS. & BAL. -- 'Anatolian' Thyme	<i>Shoot</i>	0-26
<i>Satureja cuneifolia</i> TEN. -- Cuneate Turkish Savory	<i>Shoot</i>	0-25
<i>Satureja montana</i> L. -- Winter Savory	<i>Plant</i>	0.6-25
<i>Salvia sclarea</i> L. -- Clary Sage	<i>Plant</i>	12
<i>Ocimum gratissimum</i> L. -- Agbo, Shrubby Basil	<i>Shoot</i>	0-23
<i>Coridothymus capitatus</i> (L.) REICHB. F. -- Spanish Oregano	<i>Shoot</i>	0-22
<i>Ageratum conyzoides</i> L. -- Mexican ageratum	<i>Shoot</i>	0-20
<i>Citrus aurantium</i> L. -- Petitgrain	<i>Leaf</i>	10
<i>Citrus sinensis</i> (L.) OSBECK -- Orange	<i>Fruit</i>	10
<i>Daucus carota</i> L. -- Carrot	<i>Seed</i>	10
<i>Lavandula x hybrida</i> BALB. EX GING. -- Hybrid Lavender	<i>Shoot</i>	10-17
<i>Origanum vulgare var. hirtum</i> (LINK) IETSWAART -- Istanbul Kekigi, Turkish Oregano	<i>Plant</i>	0-15
<i>Micromeria fruticosa subsp. barbata</i> (BOISS. & KY.) P.H. DAVIS -- Tea Hyssop, Zopha, Zuta	<i>Shoot</i>	0-12
<i>Sideritis germanicolpitana</i> BORNM	<i>Plant</i>	10-11
<i>Micromeria croatica</i>	<i>Leaf</i>	0-10
<i>Micromeria fruticosa subsp. barbata</i> (BOISS. & KY.) P.H. DAVIS -- Tea Hyssop, Zopha, Zuta	<i>Shoot</i>	0-10
<i>Salvia dorisiana</i> STANDL. -- 'Honduran' Sage	<i>Shoot</i>	8.6-10
<i>Sideritis mugronensis</i>	<i>Flower</i>	5-10
<i>Sideritis pauli</i> PAU -- El Molinillo Sideritis	<i>Shoot</i>	0-10
<i>Teucrium gnaphalodes</i> L'HER. -- Iberian Germander	<i>Shoot</i>	0-10
<i>Thymus zygis</i> L. -- Spanish Thyme	<i>Shoot</i>	0-10
<i>Hedeoma hispida</i> PURSH. -- Hispid Pennyroyal	<i>Plant</i>	4
<i>Monarda didyma</i> L. -- Beebalm, Oswego Tea	<i>Flower</i>	4

Ethnobotanical and Phytochemical Database Results for Terpinolene (Continued)

Species	Part	Quantity (ppm)
<i>Thymus funkii</i> COUSS. -- Funk's Thyme	<i>Shoot</i>	0-7
<i>Hyptis suaveolens</i> POIT. -- Wild Hops	<i>Shoot</i>	0-6
<i>Elsholtzia polystachya</i> BENTH. -- Bush Mint	<i>Leaf</i>	0-5.8
<i>Teucrium polium</i> var. <i>valentinum</i> -- Golden Germander, Iberian Golden Germander	<i>Shoot</i>	0-5
<i>Origanum sipyleum</i> L. -- Bayircayi, Guveyoto	<i>Shoot</i>	0-4
<i>Micromeria congesta</i> BOISS. & HAUSSKN. -- Kaya Yarpuzu	<i>Leaf</i>	0-3
<i>Micromeria thymifolia</i>	<i>Leaf</i>	0-3
<i>Micromeria varia</i> subsp. <i>thymoides</i> -- Madeiran 'Hyssop'	<i>Shoot</i>	0-3
<i>Thymus longicaulis</i> C. PRESL -- Kekik, Tas Kekik	<i>Shoot</i>	0-3
<i>Trichostemma dichotomum</i> L. -- Blue Curls	<i>Shoot</i>	0-3
<i>Hyptis suaveolens</i> POIT. -- Wild Hops	<i>Shoot</i>	0-2.5
<i>Leonotis leonurus</i> (L.) R. BR. -- Lion's Ear	<i>Se</i>	0-2
<i>Mentha aquatica</i> L. -- Water Mint	<i>Shoot</i>	0-2
<i>Myrtus communis</i> L. -- Myrtle	<i>Plant</i>	1
<i>Thymus mastichina</i> L. -- Spanish Marjoram	<i>Plant</i>	1
<i>Origanum sipyleum</i> L. -- Bayircayi, Guveyoto	<i>Shoot</i>	0-1.8
<i>Cleonia lusitanica</i> (L.) L. -- Spanish Heal-All	<i>Leaf</i>	0-1
<i>Mentha aquatica</i> L. -- Water Mint	<i>Shoot</i>	0-1
<i>Origanum vulgare</i> L. -- Common Turkish Oregano, Wild Oregano	<i>Plant</i>	0-1
<i>Calamintha nepeta</i> subsp. <i>glandulosa</i> (REQ.) P.W.BALL -- Turkish Calamint	<i>Shoot</i>	ND
<i>Acinos alpinus</i> var. <i>meridionalis</i> (NYMAN) P.W.BALL -- Te de Sierra Nevada	<i>Shoot</i>	ND
<i>Citrus mitis</i> BLANCO -- Calamansi, Calamondin	<i>Fruit Juice</i>	ND
<i>Micromeria myrtifolia</i> BOISS. & HOHEN -- Dagcayi, Haydarotu, Topukcayi	<i>Shoot</i>	ND
<i>Acorus calamus</i> L. -- Sweetflag	<i>Rhizome</i>	ND
<i>Aloysia triphylla</i> (L'HER.) BRITTON -- Lemon Verbena	<i>Plant</i>	ND

Ethnobotanical and Phytochemical Database Results for Terpinolene (Continued)

Species	Part	Quantity (ppm)
<i>Artemisia capillaris</i> THUNB. -- Capillary Wormwood	<i>Essential Oil</i>	ND
<i>Boswellia sacra</i> FLUECK -- Frankincense, Olibanum	<i>Essential Oil</i>	ND
<i>Capsicum annuum</i> L. -- Bell Pepper	<i>Fruit</i>	ND
<i>Carica papaya</i> L. -- Papaya	<i>Fruit</i>	ND
<i>Carum carvi</i> L. -- Caraway	<i>Fruit</i>	ND
<i>Cinnamomum aromaticum</i> NEES -- Cassia	<i>Plant</i>	ND
<i>Citrus aurantium</i> L. -- Petitgrain	<i>Pericarp</i>	ND
	<i>Plant</i>	ND
<i>Dictamnus albus</i> L. -- Akgiritotu, Burning Bush, Dittany, Gas Plant, Gazelotu	<i>Shoot</i>	ND
<i>Elsholtzia polystachya</i> BENTH. -- Bush Mint	<i>Leaf</i>	ND
<i>Ferula gummosa</i> BOISS. -- Galbanum	<i>Gum</i>	ND
<i>Juniperus sabina</i> L. -- Sabine	<i>Plant</i>	ND
<i>Juniperus virginiana</i> L. -- Red Cedar	<i>Leaf</i>	ND
<i>Mentha spicata</i> L. -- Hortela da Folha Miuda, Spearmint	<i>Leaf</i>	ND
<i>Mentha x piperita</i> subsp. <i>nothosubsp. piperita</i> -- Peppermint	<i>Leaf</i>	ND
<i>Micromeria fruticosa</i> -- Tasnanesi	<i>Leaf</i>	ND
<i>Micromeria varia</i> subsp. <i>thymoides</i> -- Madeiran 'Hyssop'	<i>Shoot</i>	ND
<i>Ocimum kilimandscharicum</i> GUERKE -- African Blue Basil, Kenyan Perennial Basil	<i>Plant</i>	ND
<i>Origanum syriacum</i> L. -- Za'Atar	<i>Shoot</i>	ND
<i>Origanum vulgare</i> subsp. <i>hirtum</i> (LINK) IETSWAART -- Common Turkish Oregano, Greek Oregano, Wild Oregano	<i>Shoot</i>	ND
<i>Origanum vulgare</i> var. <i>gracile</i> (C. KOCH) IETSWAART -- Slender Turkish Oregano	<i>Plant</i>	ND
<i>Origanum vulgare</i> var. <i>viride</i> (BOISS.) HAYEK -- Green Turkish Oregano	<i>Plant</i>	ND
<i>Piper nigrum</i> L. -- Black Pepper	<i>Fruit</i>	ND
<i>Prunus armeniaca</i> L. -- Apricot	<i>Essential Oil</i>	ND
<i>Ribes nigrum</i> L. -- Black Currant	<i>Fruit</i>	ND

Ethnobotanical and Phytochemical Database Results for Terpinolene (Continued)

Species	Part	Quantity (ppm)
<i>Salvia canariensis</i> L. -- Canary Island Sage	<i>Leaf</i>	ND
<i>Satureja obovata</i> LAG. -- Iberian Savory, Savory	<i>Leaf</i>	ND
<i>Thymus funkii</i> COUSS. -- Funk's Thyme	<i>Shoot</i>	ND
<i>Thymus longicaulis</i> C. PRESL -- Kekik, Tas Kekik	<i>Shoot</i>	ND
<i>Thymus orospedanus</i> H. del VILLAR -- Orosped Thyme	<i>Plant</i>	ND
<i>Valeriana officinalis</i> L. -- Common Valerian, Garden-Heliotrope, Valerian	<i>Root</i>	ND

*References may be found at Phytochemical and Ethnobotanical Database site located at
<http://www.ars-grin.gov/cgi-bin/duke/>